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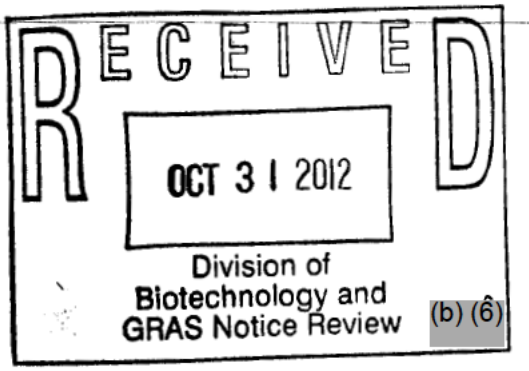

GRAS Exemption Claim for the Complexation Products of Sodium Tartrates with Iron(III) Chloride

Submitted for:

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
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June 26, 2012

GRAS Exemption Claim for the Complexation Products of Sodium Tartrates with Iron(III) Chloride

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I GRAS EXEMPTION CLAIM

I.A Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997) (U.S. FDA, 1997)]

The ingredient, defined as the complexation products of sodium tartrates with iron(III) chloride has been determined to be Generally Recognized as Safe (GRAS) by Akzo Nobel Industrial Chemicals BV (Akzo Nobel) for use as an anti-caking agent in salt in the United States (U.S.), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections. Therefore, the use of the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt for conventional food use as described below is exempt from the requirement of premarket approval.

Signed,

(b) (6)

October 11, 2012
Date

Groupfead CSL, Research sBU Salt

I.B Name and Address of Notifier

Jan Meijer
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The Netherlands

I.C Common Name of the Notified Substance

Complexation products of sodium tartrates with iron(III) chloride

I.D Conditions of Intended Use in Food

I.D.1 Intended Use of the Complexation Products of Sodium Tartrates with Iron(III) Chloride

Akzo Nobel intends to market the ingredient, defined as the complexation products of sodium tartrates with iron(III) chloride for use as an anti-caking agent in salt. The characteristics of the anti-caking agent, which is produced under specific conditions, and its intended use and use-levels are summarized in Table I.D.1-1. The amount added to salt will be that required to produce its intended effect but not in excess of 12 ppm (0.0012%) calculated as iron.

The complexation products of sodium tartrates with iron(III) chloride will be used as a replacement for, and not in addition to, other substances commonly used as anti-caking agents in salt (*i.e.*, sodium ferrocyanide decahydrate; 21 CFR §172.490 – U.S. FDA, 2012). At the levels of intended use, the anti-caking agent will not impart significant color to the salt and in accordance with the color additive exemption in 21 CFR §70.3(g) (U.S. FDA, 2012), will be used solely for its technological function in preventing caking. Any incidental coloring imparted to the salt or finished food will not contribute to the value, marketability or consumer acceptance of the food, and may in fact be undesirable. Although, this notification pertains only to salt for human consumption (food), the anti-caking agent will form an integral part of industrial salt processing intended for all common uses (road salt, food, animal feed, *etc.*) and food manufacturers will have no incentive to use the complexation products of sodium tartrates with iron(III) chloride as a color. Akzo Nobel will take appropriate measures, *e.g.*, labeling statement, to advise manufacturers of the non-color use limitations for use for the complexation products of sodium tartrates with iron(III) chloride.

Table I.D.1-1 Summary of the Characteristics and Intended Use of the Complexation Products of Sodium Tartrates with Iron(III) Chloride

Complexation Products Characteristics	
Ratio of iron(III) to *meso*-tartrate	*ca.* 1:1 (molar basis)
Ratio of iron(III) to total tartrates (*i.e.*, equilibrium mixture of DL- and *meso*-tartrates)	*ca.* 1:1.5 (molar basis)
meso-Tartrate content	*ca.* 65% of total tartrates content (*i.e.*, equilibrium mixture of DL- and *meso*-tartrates)
Intended Use-level in Salt	
Iron(III)	The amount required to achieve the desired effect; typically in the region of 3 ppm and not to exceed 12 ppm calculated as iron
meso-Tartrate	3 ppm iron(III) equivalent to 8 ppm *meso*-tartrate 12 ppm iron(III) equivalent to 33 ppm *meso*-tartrate
Total tartrates (*i.e.*, equilibrium mixture of DL- and *meso*-tartrates)	3 ppm iron(III) equivalent to 12 ppm total tartrates 12 ppm iron(III) equivalent to 47 ppm total tartrates
Complexation products of sodium tartrates with iron(III) chloride	3 ppm iron(III) equivalent to 26 ppm complexation products (calculated on dry basis) 12 ppm Fe equivalent to 106 ppm complexation products (calculated on dry basis)

I.D.2 Estimated Consumption of the Complexation Products of Sodium Tartrates with Iron(III) Chloride from Intended Food Use

The potential exposure by the U.S. population to the anti-caking agent from its addition to salt was calculated from salt intakes estimates published by the National Cancer Institute (NCI, 2010). The NCI used the 2005-2006 National Health and Nutrition Examination Survey (NHANES) to determine the specific contribution by individual foods to the total intakes of sodium, and indirectly salt, by the American population (CDC, 2009; USDA, 2009). Mean salt intakes across all population groups were determined to be 8.6 g/person/day, with mean values of 7.8 g/person/day reported for 2 to 18 year olds and 8.84 g/person/day for adults over 19 years of age. The highest mean estimated exposure to salt across the whole population (males and females) was by adults between 19 and 30 years in age at 9.54 g/person/day, and within the individual population groups by males between 19 and 30 years of age at 11.31 g/person/day. The lowest mean estimated exposure to salt was by females between 2 and 3 years of age at 5.15 g/person/day.

These data were generated from the NHANES using the composition of foods consumed during two-dietary recalls. Dietary studies, such as this one, tend to overestimate true intakes of sodium, and therefore salt, due to the inability to account precisely for added salt and the fact that much salt is discarded with the cooking water. Salt also may be lost during the cooking of manufactured foods. It is generally recommended that measurements of sodium excretion are made to determine sodium intakes more accurately. Moreover, it is well-established that short-term surveys based on dietary intake data may over-estimate the consumption of food products

that are consumed infrequently, particularly when weighted over 2-dietary recalls as per the U.S. NHANES study. While commercial salt would be the primary contributor to sodium intakes by the American population, these calculations make no adjustment for the natural occurrence of sodium in foods.

For the purposes of this assessment, to determine potential exposure by the general population to the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt, no further refinement of the salt intake estimates was considered necessary. These mean estimated salt intakes, calculated on the basis of reported sodium consumption, were used to determine the potential exposure by the general population to the complexation products of sodium tartrates with iron(III) chloride, and its major components, *meso*-tartaric acid, total tartaric acid, and iron(III). These calculations are summarized in Table I.D.2-1 and assumed that all sodium was consumed as salt by the general population, and that all salt contained the anti-caking agent at levels of either 3 ppm or 12 ppm, calculated as iron.

Of the different population groups, males between 19 and 30 years of age were determined to have the greatest daily intakes of salt on an absolute basis. Considering the worst-case scenario, where all salt consumed by this population group contained the complexation products of sodium tartrates with iron(III) chloride at the maximum level of intended use-level of 12 ppm calculated as iron, exposure to the ingredient was observed to be 1.20 mg/person/day equivalent to iron(III) and total tartrates intakes of 0.14 and 0.53 mg/person/day, respectively. On a body weight basis, the corresponding exposure by a male adult of 70 kg was 0.017 mg/kg body weight/day for the complexation products of sodium tartrates with iron(III) chloride, 0.002 mg/kg body weight/day for iron(III) and 0.008 mg/kg body weight/day for total tartrates.

In children or young people (2 to 18 years), the greatest exposure on an absolute basis was observed in males. Considering the worst case scenario, where all salt consumed by this population group contained the complexation products of sodium tartrates with iron(III) chloride at the maximum intended use-level of 12 ppm calculated as iron, exposure to the ingredient was observed to be 0.92 mg/person/day, equivalent to iron(III) and total tartrates intakes of 0.10 and 0.41 mg/person/day, respectively. Body weights will vary considerable across this population group, but as an approximation, the corresponding exposure by a male child of 30 kg was determined to be 0.03 mg/kg body weight/day for the complexation products of sodium tartrate with iron(III) chloride, 0.003 mg/kg body weight/day for iron(III), and 0.014 mg/kg body weight/day for total tartrates.

Table I.D.2-1 Estimated Intakes of the Complexation Products of Sodium Tartrates with Iron(III) Chloride from Its Use as an Anti-Caking Agent in the U.S.

Population Group (Estimated Salt Intake)	Equivalent Intake (mg/person/day)							
	Level: 3 ppm Calculated as Iron				Level: 12 ppm Calculated as Iron			
	Complexation Products (Total)	*meso*-Tartrate	Total Tartrates	Iron(III)	Complexation Products (Total)	*meso*-Tartrate	Total Tartrates	Iron(III)
All Persons								
Young people 2-18 years (7.8 g/day)	0.21	0.07	0.09	0.02	0.83	0.26	0.37	0.09
Adults 19+ years (8.8 g/day)	0.23	0.07	0.10	0.03	0.94	0.30	0.42	0.11
All Males								
Young people 2-18 years (8.7 g/day)	0.23	0.07	0.10	0.03	0.92	0.29	0.41	0.10
Adults 19+ years (10.5 g/day)	0.28	0.09	0.12	0.03	1.11	0.35	0.49	0.13
Adults 19-30 years (11.3 g/day)[1]	0.30	0.09	0.13	0.03	1.20	0.38	0.53	0.14
All Females								
Young people 2-18 years (7.2 g/day)	0.18	0.06	0.08	0.02	0.73	0.23	0.33	0.08
Adults 19+ years (7.6 g/day)	0.19	0.06	0.09	0.02	0.78	0.24	0.35	0.09

[1] These data are included in addition to young people and adults 19 years of age and above because they reflect the greatest intakes on a g per day basis of all population groups.

As briefly outlined above, this type of methodology may be considered to over-estimate the true exposure to commercial (added) salt in foods by the general U.S. population. Moreover, in practical terms, it is highly unlikely that an individual would consume only salt containing the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent or that it would be always be added at the maximum use-level of 12 ppm calculated as iron. For the purposes of the safety assessment, however, these conservative estimates of exposure to the complexation products of sodium tartrates with iron(III) chlorides were considered sufficient. In Section IV, the toxicological information are assessed on the basis that an individual would not consume more than 11.3 g of salt containing the complexation products of sodium tartrates with iron(III) chloride at 12 ppm calculated as iron (row shaded in grey in Table I.D.2-1).

I.E Basis for the GRAS Determination

Pursuant to Title 21, Section 170.30 of the *Code of Federal Regulations* (CFR) (U.S. FDA, 2012), the complexation products of sodium tartrates with iron(III) chloride have been determined to be GRAS on the basis of scientific procedures. This GRAS determination is based on data generally available in the public domain pertaining to the safety of the complexation products of sodium tartrates with iron(III) chloride, as discussed herein, and on consensus among a panel of experts who are qualified by scientific training and experience to evaluate the safety of the ingredient as a component of food [see Appendix A, entitled "Expert Panel Consensus Statement Concerning the GRAS Status of the Reaction Products of Sodium Tartrates and Iron(III) Chloride for Use in Foods"].

At the request of Akzo Nobel, an Expert Panel ("the Expert Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended use of the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt is safe and suitable and would be GRAS based on scientific procedures.

The Panel consisted of the following qualified scientific experts: Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor John A. Thomas, Ph.D. (Indiana University School of Medicine), and Professor Robert Nicolosi (University of Massachusetts-Lowell).

The Expert Panel convened on behalf of Akzo Nobel independently and collectively, and critically evaluated the data and information summarized herein and concluded that the intended use in traditional foods described herein for the complexation products of sodium tartrates with iron(III) chloride, meeting appropriate food-grade specifications and manufactured according to current Good Manufacturing Practice (cGMP), is safe, suitable, and GRAS based on scientific procedures. It also is the Expert Panel's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion.

The ingredient defined as the complexation products of sodium tartrates with iron(III) chloride is GRAS based on scientific procedures for its intended use as a food ingredient; therefore, it is excluded from the definition of a food additive, and thus, may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

I.F Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the FDA upon request, or will be available for review and copying at reasonable times at the offices of:

Akzo Nobel Industrial Chemicals BV
AkzoNobel Deventer
P.O. Box 10
7400 AA Deventer
The Netherlands

Should FDA have any questions or additional information requests regarding this notification, Akzo Nobel will supply these data and information.

II. DETAILED INFORMATION ABOUT THE SOURCE AND IDENTITY OF THE SUBSTANCE

II.A Identity

The anti-caking agent is the complexation products formed on combining an equilibrium mixture of sodium tartrates [DL- and *meso*-tartaric acid] with iron(III) chloride under specified conditions (see Table I.D.1-1 and Section II.B). The identity of the anti-caking agent is summarized in Table II.A-1.

Table II.A-1 Identity of the Complexation Products of Sodium Tartrates with Iron(III) Chloride

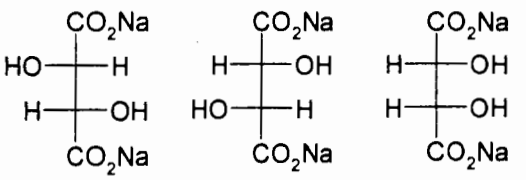
Parameter	Identification
Common name	Complexation products of sodium tartrates with iron(III) chloride
Chemical names	Iron(III) complexation products of D(+) -, L(-)- and meso-2,3-dihydroxbutanedioc acids
Chemical structures	Complexation products of FeCl3 with:  D(-)-tartrate L(-)-tartrate *meso*-tartrate
European Commission (EC) Number	700-459-3
Chemical Abstract Services (CAS) Number	None assigned
Physical state	Dark green aqueous solution (ca. 35% w/w anti-caking agent)

Table II.A-1 Identity of the Complexation Products of Sodium Tartrates with Iron(III) Chloride	
Density of solution at 20 °C	1.265 gcm-3
pH	3.5-3.8

II.B Method of Manufacture

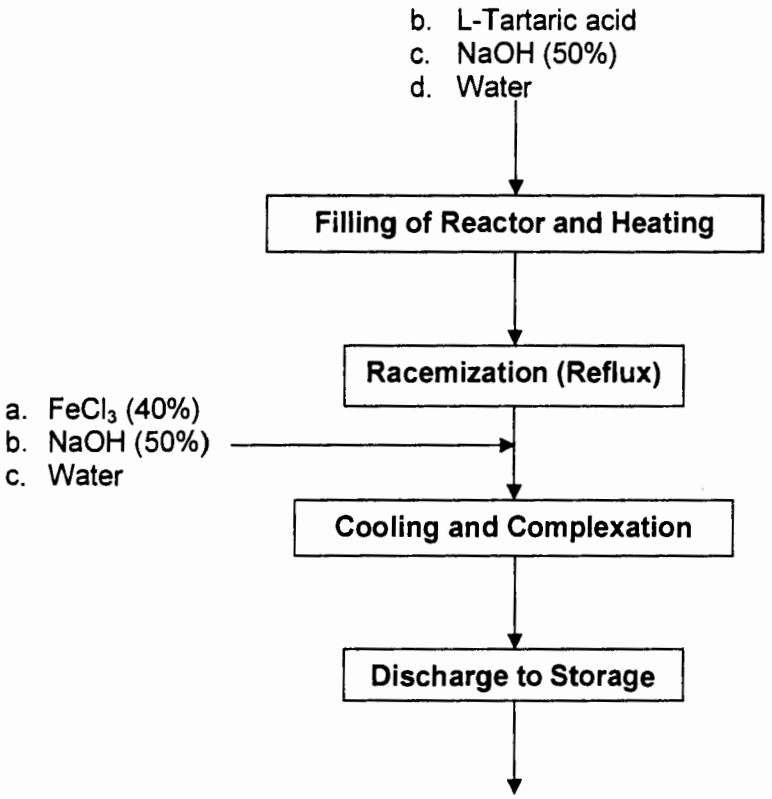
All raw materials and processing aids employed in the manufacture of the complexation products of sodium tartrates with iron(III) chloride are used in accordance with applicable U.S. federal regulations, and/or are permitted for use in food as described in Table II.B-1.

Table II.B-1 Raw Materials Used in the Manufacture of the Complexation Products of Sodium Tartrates with Iron(III) Chloride

Material	Use	Regulatory Status
Iron(III) chloride	Source of iron(III)	GRAS when used in accordance with cGMP for use as a flavoring agent (21 CFR §184.1297 – U.S. FDA, 2012)
L-Tartaric acid	Source of tartrates	L-Tartaric acid is GRAS when used in accordance with cGMP for use in foods as a firming agent, flavor enhancer, humectants or pH control agent (21 CFR §184.1099 – U.S. FDA, 2012); potassium acid L-tartrate, sodium L-tartrate and sodium potassium L-tartrate are affirmed as GRAS for use as anti-caking agents, anti-microbial agents, formulation aids, humectants, leavening agents, pH control agents, processing aids, stabilizers, thickeners and surface-active agents for use in various food categories (21 CFR §184.1077, §184.1801, and §184.1804 – U.S. FDA, 2012)
Sodium hydroxide	Processing aid (base)	GRAS when used in accordance with cGMP for use in foods as a pH control agent and processing aid (21 CFR §184.1763 – U.S. FDA, 2012)

An overview of the manufacturing process to the complexation products of sodium tartrates with iron(III) chloride is provided in Figure II.B.1-1. An aqueous solution of L-tartaric acid is heated to reflux in the presence of sodium hydroxide to achieve isomerization affording an equilibrium mixture of DL- and *meso*-tartrates (*ca.* 0.5:1 on a molar basis, equivalent to *meso*-tartrate representing around 65% of the total tartrates content). On cooling, an aqueous solution of iron(III) chloride is added to the equilibrium mixture of sodium tartrates with a concomitant color change to dark green, indicative of complex formation. The levels of addition are equivalent to approximately 1.5 moles total tartrates (all isomers) and 1 mole of *meso*-tartrate per mole of iron(III) chloride. The pH of the resultant solution is maintained at 3.7 ± 0.1 by the addition of an aqueous sodium hydroxide as necessary to ensure the consistency of the final product. This solution meeting the specifications summarized in Table II.B-2 is considered the anti-caking agent [*i.e.*, the complexation products of sodium tartrates with iron(III) chloride] and the subject of this notification. At the point of use, the solution defined as the anti-caking agent would be diluted approximately 8-fold with water and distributed over salt on a transport belt under a fluid distributor.

Figure II.B-1 Schematic of the Manufacturing Process to the Complexation Products of Sodium Tartrates with Iron(III) Chloride



Final Product: Complexation products of sodium tartrates with iron(III) chloride (*ca.* 35% w/w aqueous solution; pH 3.7± 0.1)

Table II.B-2 Manufacturing Specifications for the Complexation Products of Sodium Tartrates with Iron(III) Chloride (*ca.* 35% Aqueous Solution)

Parameter	Specification	Method of Analysis
meso-Tartrate	Not less than 10%	HPLC
DL-Tartrate	Not less than 3%	HPLC
Iron(III)	Not less than 3%	Spectrophotometry
pH	3.5 to 3.9	pH meter
Oxalates (impurity), calculated as oxalic acid	Not more than 0.5%	HPLC

HPLC = high performance liquid chromatography.

II.C Product Specifications and Analytical Data

The anti-caking agent, defined by its specific molar ratios of iron to *meso*-tartrate (1:1) and iron to total tartrates (1:1.5), is manufactured as an aqueous solution (*ca.* 35% complexation products of sodium tartrates with iron(III) chloride by weight; see Table II.B-2) which is further diluted at the point of addition to salt (*ca.* 8-fold). For standardization purposes, product specifications are provided for each of the key constituents calculated on a dry weight basis (Table II.C-1). The purity criteria are consistent, where relevant, with those laid down by the Food Chemicals Codex (FCC) for the sodium and potassium salts of L-tartaric acid (FCC, 2010).

Table III.C-1 Product Specifications for the Complexation Products of Sodium Tartrates with Iron(III) Chloride

Parameter		Proposed Specification	Method of Analysis
Definition			
Chemical name		Complexation products of sodium tartrates with iron(III) chloride	-
Chemical formula		$Fe(OH)_2C_4H_4O_6Na$ (nominal)	-
Molecular weight		261.93 (nominal)	-
Assay	*meso*-Tartrate	Not less than 37%, calculated as disodium salt on dry basis	IC (anion)
	DL-Tartrate	Not less than 14%, calculated as disodium salt on dry basis	IC (anion)
	Iron(III)	Not less than 8%, calculated as element on dry basis	ICP-ES
Description		Dark green aqueous solution typically comprising *ca.* 35% by weight complexation products with a pH of between 3.5 and 3.9	Visual inspection; pH meter
Identification		Passes tests for tartrate and iron	FCC; Appendix IIIA (passes test)
Purity			
Water		Not less than 65%	Loss on drying
Chloride		Not more than 25% on dry basis	Titration
Sodium		Not more than 23% on dry basis	ICP-ES
Arsenic		Not more than 3 ppm	ISO 11885
Lead		Not more than 5 ppm	ISO 11885
Mercury		Not more than 1 ppm	ISO 11885
Oxalates		Not more than 1.5%, calculated as oxalic acid on dry basis	IC (anion)

IC = ion chromatography; ICP-ES = inductively coupled plasma – emission spectroscopy.

The relative proportions of the components of the anti-caking agent are confirmed analytically for 3 non-consecutive lots to yield a consistent product that meets the manufacturing and product specifications (Tables II.B-2 and II.C-1, respectively). Analytical data also demonstrate the absence of any manufacturing impurities or external contaminants at levels of potential toxicological concern. Microbiological specifications are not considered necessary on the basis

that microbial growth would not be sustained under the highly alkaline conditions of the manufacturing process or intended use as an anti-caking agent in salt.

Table III.C-2 Relative Proportions of Each Component of the Complexation Products of Sodium Tartrates with Iron(III) Chloride (ca. 35% w/w Aqueous Solution)

Component	Calculated Concentrations (CV in %)[1,2]		
	Batch 1	Batch 2	Batch 3
D-Tartaric acid, disodium salt	5.1 ± 0.3 (5)	5.9 ± 0.3 (5)	5.6 ± 0.3 (5)
L-Tartaric acid, disodium salt			
meso-Tartaric acid, disodium salt	13.8 ± 0.7 (5)	13.2 ± 0.7 (5)	13.5 ± 0.7 (5)
Oxalic acid, disodium salt (impurity)	0.3 ± 0.02 (5)	0.5 ± 0.03 (5)	0.3 ± 0.02 (5)
Iron(III)	3.7 ± 0.2 (5)	3.7 ± 0.5 (5)	3.7 ± 0.2 (5)
Chloride	7.2 ± 0.1 (2)	7.2 ± 0.1 (2)	7.2 ± 0.1 (2)
Sodium	2.4 ± 0.1 (5)	2.4 ± 0.1 (5)	2.3 ± 0.1 (5)
Hydroxide[3]	1.7	1.8	1.6
Water	66.1 ± 0.01 (0.1)	65.8 ± 0.7 (0.1)	66.9 ± 0.07 (0.1)
Total (mass balance)[4]	*100.3 ($S_R \approx 0.8$)*	*100.5 ($S_R \approx 0.8$)*	*101.1 ($S_R \approx 0.8$)*

CV = coefficient of variation; S_R = standard deviation under reproducibility conditions;
[1] Chloride concentration in excess to iron ions expressed as sodium chloride, tartrates and oxalate expressed as disodium salts, remaining sodium expressed as sodium hydroxide but in practice will react with various acidic components present in mixture;
[2] Errors determined as approximate standard deviation (S_R) only;
[3] Back-calculation only;
[4] 95% Confidence interval for the mass balance (one single determination, n =1) for batches analyzed under reproducibility conditions 98.9-102.1 w/w%.

Negative ion mass spectrometry, ultra violet-visible spectroscopy and infra-red spectroscopy also may be used for characterization purposes. The spectra obtained by these techniques exhibit features characteristic of iron/tartrates or carboxylic acid species and consistent with the anti-caking agent, as defined.

II.D Stability Data

The degradation of carboxylic acids, including L-tartaric acid in the presence of trace levels of iron(III) is well established to occur by photochemistry and Fenton chemistry (Abrahamson *et al.*, 1994; Clark *et al.*, 2007). Similar degradation processes would be anticipated to occur in the complexation products of sodium tartrates with iron(III) chloride and would apply generally D-, L- and *meso*-tartrates. Akzo Nobel has been successfully storing and transporting the anti-caking agent, as defined herein, for use in salt for industrial purposes for a number of years, and the appropriate storage and transport conditions are well established along with suitable indicators of degradation (Table II.D-1).

Table II.D-1 Indicators of Degradation	
Factor	**Potential Role as Indicator of Stability**
pH	Changes in pH may be indicative of degradation or precipitation of tartaric acid from solution
Solution color	Color changes may be indicative of degradation or precipitation of Fe/tartrate species from solution
Crystallization	Formation of crystals indicative of precipitation of species from solution (*e.g.*, Fe/tartrates, iron hydroxide species)
Content of constituents	Specific concentration of individual constituents may be indicative of degradation or precipitation from solution
Fe(II) content	Fe(II) content indicates reduction of Fe(III); often Fe(II) content may oscillate consistent with Fe(II)/Fe(III) equilibria in solution (Fenton chemistry)
Oxalate content	Increased levels of oxalate may be used as an indicator for decomposition of tartaric acid
Gas production	Formation of gas bubbles is indicative of oxidative decarboxylation of tartaric acid

The results of a 6-month study in which the complexation products of sodium tartrates with iron(III) chloride were stored at room temperature (20°C) under conditions of varying pH and sunlight exposure indicated that:

a. Solutions of the complexation products of sodium tartrates with iron(III) chloride stored in the dark at room temperature as manufactured [*ca.* 35% w/w aqueous solution; iron(III) *ca.* 4.2%] or diluted [*ca.* 8-fold; iron(III) *ca.* 0.58%] were stable for up to 3 months;

b. Solutions of the complexation products of sodium tartrates with iron(III) chloride stored in sunlight at room temperature as manufactured [*ca.* 35% w/w aqueous solution; iron(III) *ca.* 4.2%] or diluted [*ca.* 8-fold; iron(III) *ca.* 0.58%] were not stable and decomposition occurred within days.

The results of a 3-month study in which the complexation products of sodium tartrates with iron(III) chloride were stored in the dark at varying temperatures indicated that:

a. No crystallization or significant decomposition occurred in solutions of the complexation products of sodium tartrates with iron(III) chloride stored at 10°C as manufactured [*ca.* 35% w/w aqueous solution; iron(III) *ca.* 4.2%] or diluted [*ca.* 8-fold; iron(III) *ca.* 0.58%]; microbial growth was only observed in the diluted solution (attributed to the greater water content);

b. Crystallization and degradation was observed in solutions of the complexation products of sodium tartrates with iron(III) chloride stored at 60°C both as manufactured [*ca.* 35% w/w aqueous solution; iron(III) *ca.* 4.2%] and diluted [*ca.* 8-fold; iron(III) *ca.* 0.58%]; microbial growth was apparently detected in the diluted solution (attributed to the greater water content);

c. Some crystallization and degradation was observed in solutions of the complexation products of sodium tartrates with iron(III) chloride stored at 60°C for 1 week and 10°C for 3 months, as manufactured [*ca.* 35% w/w aqueous solution; iron(III) *ca.* 4.2%] but not diluted [*ca.* 8-fold; iron(III) *ca.* 0.58%]; no microbial growth was observed in either of the solutions.

Any degradation of the anti-caking agent following application on the salt would be expected to occur by the established pathways above, albeit at a slower rate than in solution, and be readily identified by loss of effect, *i.e.*, caking of the salt. Analytical data demonstrating the ability of the anti-caking agent, as defined herein, to function in salt under the conditions of intended use have been described in detail in a patent application by Akzo Nobel (Bakkenes *et al.*, 2010). The results reported in the patent application demonstrate that under conditions typical of the intended use in salt (3 ppm calculated as iron), an anti-caking agent with specific molar ratios of iron to *meso*-tartrate and total tartrates of 1:1 and 1:1.5, respectively as defined herein, is more effective than species with different iron to tartrates ratios and the established anti-caking agent, sodium ferrocyanide decahydrate.

III. SELF-LIMITING LEVELS OF USE

The ability of the complexation products of sodium tartrates with iron(III) chloride to act as an anti-caking agent provides a self-limiting level of use on the basis that there would be no technological advantages, and may be disadvantages, to using higher levels than those required to achieve the desired effect in salt.

IV. BASIS FOR GRAS DETERMINATION

IV.A Documentation to Support the Safety of the Complexation Products of Sodium Tartrates with Iron(III) Chloride

The determination that the complexation products of sodium tartrates with iron(III) chloride (hereafter referred to as the anti-caking agent) is GRAS is on the basis of scientific procedures. Based on its chemical properties, the anti-caking agent will dissociate to its respective components upon ingestion, namely iron(III), D-tartrate, L-tartrate, and *meso*-tartrate. Similarly, iron complexes of other dicarboxylic acids such as iron bisglycinate (EFSA, 2006) are well established to dissociate on ingestion. This behavior is confirmed by a color change of aqueous solutions of the anti-caking agent from dark green to yellow on lowering of the pH to <2 consistent with loss of the iron/tartrate interactions. Magnetic susceptibility measurements on solutions of the anti-caking agent provide additional evidence for dissociation at low pH. While solutions at pH 6 and 4 exhibit magnetic behavior consistent with complex formation (*i.e.*, iron/tartrate interactions) on lowering the pH to 2, the magnetic susceptibilities of solutions of the anti-caking agent and iron(III) chloride are comparable. Thus, the safety assessment of the

anti-caking agent under its intended conditions of use and estimated intakes is primarily based on the database of published information pertaining to the safety of the individual components, iron and tartaric acids. In addition, unpublished findings of pre-clinical toxicological studies on the anti-caking agent itself provide corroborative evidence of its safety under the intended conditions of use. As mentioned in Section IV, the toxicological information are assessed on the basis that an individual would not consume more than 11.3 g of salt containing the complexation products of sodium tartrates with iron(III) chloride at 12 ppm calculated as iron (row shaded in grey in Table I.D.2-1). Overall, the data on the identity, intended use, estimated intakes, and safety of the anti-caking agent and its constituents support the general recognition of its safety under the intended conditions of use.

IV.B Information Pertaining to the Safety of Tartrates as Components of the Anti-Caking Agent

IV.B.1 Current Uses and Background Exposure to Tartrates in the Diet

Tartaric acid, generally of the L-configuration, occurs naturally in fruit and fruit-derived products such as juices. For example, the content of tartaric acid of red grape, white grape, and pomegranate juices were determined to be 0.8, 0.9, and 3.4 mg/L, respectively (Ehling and Cole, 2011). In addition, L-tartaric acid is a direct food substance affirmed as GRAS in Title 21 of the CFR when used in accordance with cGMP as a firming agent, flavor enhancer, flavoring agent, humectants, or pH control agent (21 CFR §184.1099 – U.S. FDA, 2012). The potassium and sodium salts of L-tartaric acid are also direct food substance affirmed as GRAS with no limitations on their use other than cGMP (21 CFR §184.1077; §184.1801; §184.1804 – U.S. FDA, 2012). L-Tartaric acid may be added to foods such as fruit butter, fruit jellies, preserves and jams, artificially sweetened jellies and preserves, and in fruit sherbets (Deshpande *et al.,* 1994). It is also widely used as a flavor enhancer in grape- and lime-flavored beverages (Deshpande *et al.,* 1994). Considering the extensive permitted uses of L-tartaric acid and its salts in conventional food products, combined with its natural occurrence in fruit and fruit products, it is logical that the exposure to total tartrates (equilibrium mixture of DL- and *meso*-tartrates) from the intended use of the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt at levels not to exceed 12 ppm calculated as iron (equivalent to 47 ppm total tartrates) would not make a significant contribution to the overall background dietary intakes of L-tartaric acid.

Mixtures of L-, D-, DL-, and *meso*- forms of tartaric acid are used as flavoring agents (JECFA, 2000; Burdock, 2009). When evaluated by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food (JECFA) in 1999, the estimated daily *per capita* intakes of the isomers were 14 mg/person in the U.S. and 4.4 mg/day in Europe (JECFA, 2000). Comparatively, even under the worst case scenario of an adult consuming 11.3 g of salt per day containing the anti-caking agent at the maximum use level of

12 ppm calculated as iron, the estimated intakes of total tartrates from this source were ≤0.53 mg/person/day, significantly lower than the estimated dietary intakes of the isomers from flavoring use.

IV.B.2 Toxicological Data Supporting the Safety of Tartrates

The safety of tartaric acid and it salts (L-, DL-forms) has been evaluated in a number of pre-clinical toxicological studies. These studies were considered by JECFA and the Scientific Committee on Food (SCF) in their respective evaluations of L-tartaric acid and its salts, and the mixture of the isomers when used as food additives. The findings of the key studies, as well as their relevance to the safety assessment of Akzo Nobel's anti-caking agent under the intended conditions of use, are discussed below.

JECFA established a group acceptable daily intake (ADI) of 30 mg/kg body weight for L-tartaric acid and its sodium, potassium, and potassium sodium salts (JECFA, 1974, 1977, 1978). A no-observed-effect level (NOEL) determined for L-tartaric acid in a 2-year rat study (Fitzhugh and Nelson, 1947) was used to derive this ADI. Specifically, 1.2% L-tartaric acid in the diet, which was the highest dose evaluated and equivalent to approximately 1,200 mg/kg body weight/day, was determined as the NOEL in the study. The findings of a subsequent long-term rat study by Hunter *et al.* (1977) re-confirmed the ADI of 30 mg/kg body weight (JECFA, 1978). In this latter study, no compound-related adverse effects were reported following the dietary administration of up 7.68% monosodium L-tartrate (equivalent to approximately 2,600 mg tartaric acid/kg body/weight/day) for a period of 104 weeks.

In contrast, JECFA concluded that an ADI for DL-tartrate could not be established on the basis that adequate long-term studies on DL-tartrate were not available and that the DL- form of tartrate was implicated in causing kidney effects at high doses (JECFA, 1978). The findings of a series of 3 experiments conducted by Down *et al.* (1977) provided the evidence of nephrotoxicity associated with high doses of DL-tartrate. In the 3 experiments, groups of male rats were administered 2.73 g/kg body weight/day of either radiolabeled (^{14}C) monosodium L- or DL-tartrate by oral gavage for periods of up to 7 or 8 days in order to compare the metabolic fate of the two different forms of tartrate. It was observed that although the radiolabels from both forms of the tartrate salt were rapidly cleared from most tissues once the dosing period ceased, the DL-tartrate radiolabel persisted in the kidney for a longer period of time (*i.e.*, indicative of DL-tartrate precipitation in the kidney). This finding was corroborated by increased relative kidney weights and histology of kidneys that revealed changes consistent with crystalluria in the animals treated with the DL- form of the tartrate salt. In contrast, the relative kidney weight and histology of the kidneys of the L-tartrate-treated animals were comparable to an untreated control group. Therefore, despite the fact that the same high dosages of L- and DL- forms of tartrate were administered, nephrotoxicity was associated only with the administration of the DL- form. This difference was attributed to the relatively poorer solubility of

the DL- form, which means it is more likely to precipitate in the renal tubules and lead to tubular nephritis when administered at such high doses.

The SCF concurred with the group ADI of 30 mg/kg body weight for L-tartaric acid and its salts established by the previous JECFA evaluations (SCF, 1991a,b). Similarly, the SCF concluded that there are insufficient data to establish an ADI for DL-tartrate. Since the latest evaluations by JECFA and the SCF, no new data contradicting the conclusions reached by these authoritative bodies were identified.

It is important to note that under the proposed conditions of use the anti-caking agent, the resulting exposure to total tartrates (35% DL- and 65% *meso*- forms; Table I.D.2-1) on a body weight basis would be negligible when compared to the dosage of DL-tartrate associated with nephrotoxicity in the studies conducted by Down *et al.* (1977) (*i.e.,* ≤ 7.6 µg/kg body weight/day of total tartrates for a 70 kg individual *vs.* 2,730 mg/kg body weight/day). The nephrotoxic effects are expected to be dose-dependent and therefore, would not be anticipated as a result of exposure to total tartrates as a component of the anti-caking agent under its intended conditions of use. This is corroborated by the findings of a combined 90-day toxicity and reproduction/developmental toxicity rat study on Akzo Nobel's anti-caking agent itself (presented in Section IV.D) wherein renal effects were dose-dependent with compound-related renal effects not observed in rats administered up to the mid-dose of 1,000 mg anti-caking agent/kg body weight/day (which provided 443 mg/kg body weight/day of total tartrates) but observed in the high dose group of 2,000 mg anti-caking agent/kg body weight/day (increased relative kidney weights).

In 1999, JECFA evaluated mixtures of L-, D-, DL-, and *meso*- forms of tartaric acid when used as a flavoring agent (JECFA, 2000). The estimated current levels of intake of the mixture of tartaric acid were relatively low, 14 mg/day in the U.S. and 4.4 mg/day in Europe. These current intake levels were calculated to be <10,000 (U.S.) or <1,000 (Europe) times less than the NOEL of 1,200 mg L-tartaric acid/kg body weight/day determined for rats in the 2-year rat study by Fitzhugh and Nelson (JECFA, 2000). On the basis of this comparison, JECFA concluded that "there were no safety concerns at the estimated current levels of intakes" of the mixtures of L-, D-, DL-, and *meso*- forms of tartaric acid. The approach taken by JECFA to evaluate the safety of the mixture when used as a flavoring agent is indicative of: (i) at low levels of exposure to D-, DL-, and/or *meso*- forms of tartrate, data on the L-tartrate form can be extrapolated to the other forms of tartrate in order to make an informed decision pertaining to safety, because differences in metabolic fate of the varying forms would either not be expected or be as pronounced at lower levels; and (ii) nephrotoxic effects are expected to be dose-dependent and thus, the nephrotoxicity associated with relatively high doses of DL-tartrate (*i.e.,* 2.36 g/kg body weight/day) would not be anticipated at much lower levels of exposure. Therefore, considering that the resulting exposures to total tartrates as a component of the anti-caking agent under the intended conditions of use are extremely low ≤7.6 µg/kg body weight/day on a body weight

basis for a 70 kg individual), the evidence supporting the safety of L-tartrate can be used for extrapolation purposes. The estimated exposures to total tartrates, ≤7.6 µg/kg body weight/day, are relatively negligible when compared to the NOEL of 1,200 mg/kg body weight/day determined for L-tartaric acid in rats (Fitzhugh and Nelson, 1947), indicating that the likelihood of adverse effects under the proposed conditions of use of the anti-caking agent is limited.

IV.B.3 Conclusions

The resulting exposure to total tartrates (35% DL- and 65% *meso*- forms) on a body weight basis under the proposed conditions of use is not significant when compared to the background dietary intake of tartaric acid and it salts as a result of their natural occurrence in foods and/or food additive uses. The evidence supporting the safety of L-tartrate was considered appropriate for extrapolation to the very low exposures to mixtures of isomers, as would be scenario under the intended conditions of use described herein. The NOEL of 1,200 mg/kg body weight/day determined for L-tartaric acid in rats far exceeds the estimated intakes to total tartrates from the anti-caking agent under the proposed uses (≤0.53 mg/day or ≤7.6 µg/kg body weight/day for a 70 kg individual). Therefore, it is reasonable to conclude that no safety concerns would be anticipated as a result of exposure to this component of the anti-caking agent under the proposed conditions of use.

IV.C Information Pertaining to the Safety of Iron as a Component of the Anti-Caking Agent

IV.C.1 Current Uses and Background Exposure to Iron in the Diet

Iron is an essential trace mineral in human nutrition. Dietary sources of iron include legumes, green vegetables and meat. Foods may also be fortified with iron. Iron-fortified foods can be claimed "good" or "excellent" sources of iron if they contain 10 to 19% and >20%, respectively, of the Daily Value for iron per Reference Amount Customarily Consumed (RACC); the daily value (DV) for iron is 18 mg/person/day. It is noteworthy that a number of iron(III) salts is listed as a direct food substances affirmed as GRAS in Title 21 of the CFR with no limitation on their use other than cGMP, reflecting the long history of use of iron sources as food ingredients.

The Recommended Dietary Allowance (RDA) for iron is 8 mg/day for all groups of men and postmenopausal women and 18 mg/day for premenopausal women (IOM, 2001). Based on the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994), the estimated mean intake of iron from food by the U.S. population was approximately 16 to 18 mg/day for men and 12 mg/day for women; the 90th percentile intake was approximately 25 to 31 mg/day for men and 18 to 20 mg/day for women (IOM, 2001). When supplemental use was included in the calculations, the estimated mean intake of iron from food and supplements was approximately 16 to 19 mg/day for men and 12 to 13 mg/day for women; the 90th percentile

intake was approximately 26 to 35 mg/day for men and 20 to 32 mg/day for women (IOM, 2001).

As presented in Section I.D.2, considering the worst case scenario, where an individual consumes 11.3 g of salt containing the maximum intended use level of the complexation products of sodium tartrates with iron(III) chloride of 12 ppm calculated as iron, exposure to the element is estimated to be ≤0.14 mg/person/day. The overall contribution to the background dietary intakes of iron from all nutrient and additive sources would be negligible under the intended conditions of use and the risk of adverse effects as result of exposure to the iron constituent low.

IV.C.2 Tolerable Upper Intake Levels for Iron

The safety of iron and iron compounds has been extensively evaluated by various scientific committees, including the Food and Nutrition Board of the Institute of Medicine (IOM) and JECFA (JECFA, 1983, 2008a,b, 2010a,b; IOM, 2001). JECFA established a Provisional Maximum Tolerable Daily Intake (PMTDI) of 0.8 mg/kg body weight/day *(i.e.*, 56 mg/day for a 70 kg individual) for all sources of iron with the exception of iron oxides used as coloring agents, or for iron supplementation during pregnancy, lactation, or for special clinical requirements. Similarly, the IOM established a Tolerable Upper Intake Level (UL) of 45 mg/day for adults based on gastrointestinal distress as an adverse effect (IOM, 2001).

Given the low anticipated exposure by an individual to iron from the intended use of the anti-caking agent in salt (≤0.14 mg/person/day; Table I.D.2-1) and negligible contribution to background dietary intakes of the element (Section IV.C.1), there is no potential for exceeding the UL as a consequence of the intended use and therefore, the risk of adverse effects to this constituent is minimal.

IV.C.3 Conclusions

Considering that an UL of 45 mg/day is established for iron and that the estimated 90th percentile dietary intake of iron in the U.S. ranges from approximately 20 to 35 mg/day depending on the population group (IOM, 2001), the contribution of up to 0.14 mg iron/day under the intended conditions of use of the anti-caking agent is not anticipated to pose any safety concerns.

IV.D Information Pertaining to the Safety of the Anti-Caking Agent

Akzo Nobel has conducted some pre-clinical toxicological studies on the anti-caking agent, including an acute toxicity study in rats and a 90-day toxicity study combined with a 28-day reproduction and developmental toxicity study as well as a standard battery of mutagenicity and

genotoxicity tests. These studies are summarized in Table IV.D-1 and their findings and conclusions are highlighted below

An oral LD_{50} value of >2,000 mg/kg body weight, the highest dose evaluated, was determined for the anti-caking agent in female Wistar rats (van Otterdijk, 2010). Negative results for mutagenicity or genotoxicity were determined for the anti-caking agent under the experimental conditions of a standard battery of *in vitro* assays (Buskens, 2010; Verbaan, 2010; Verspeek-Rip, 2011). In the combined 90-day toxicity and reproduction/developmental toxicity study in rats, the following no-observed-adverse-effect levels (NOAEL) for anti-caking agent were determined: 500 mg/kg body weight/day for parental local toxicity; 1,000 mg/kg body weight/day for parental systemic toxicity; and at least 2,000 mg/kg body weight/day (the highest dose level tested) for both reproduction and developmental toxicity (van Otterdijk, 2011). In comparison to the lowest NOAEL determined for the anti-caking agent in this combined study, the worst case scenario exposure under the proposed conditions of use of the anti-caking agent would be considerably lower (*i.e.,* 500 mg/kg body weight/day *vs.* 1.2 mg/day or approximately 0.02 mg/kg body weight/day for a 70 kg individual).

Overall, the findings of these pre-clinical toxicological studies provide corroborative evidence of safety for the anti-caking agent under the intended conditions of use.

Table IV.D-1 Summary of Pre-Clinical Toxicological Studies on Akzo Nobel's Anti-Caking Agent [Complexation Products of Sodium Tartrates with Iron(III) Chloride]

Type of Study (Reference)	Study Details	Conclusions on Safety
In Vivo Rat Studies		
Acute oral toxicity study (van Otterdijk, 2010 – unpublished)	Two subsequent groups of female Wistar rats (3/group) were administered a single oral gavage dose of 2,000 mg/kg bw of the anti-caking agent followed by a 15-period observation period.	Oral LD_{50} >2,000 mg/kg bw (the highest dose evaluated).
90-day toxicity study combined with a 28-day reproduction and developmental toxicity study (van Otterdijk, 2011 –unpublished)	Species: Wistar Han rats No. of animals: 10/sex/group Treatment groups: 0, 500, 1,000, or 2,000 mg/kg bw/d of the anti-caking agent (control, low-, mid-, and high-dose groups, respectively) Duration: Males treated for 78 days prior to mating and during mating for a total of 90 to 91 days; Females were treated for 78 days prior to treatment, during mating and gestation, and for at least 4 days during lactation for a total of 104 to 109 days Route of administration: Oral (gavage) Evaluated parameters: Clinical signs (daily), mortality/viability, functional observations, locomotor activity, body weight (weekly), food consumption	Parental Findings: Parental toxicity at was observed at mid- and high-dose groups. Findings indicative of local toxicity including inflammatory/hyperplastic lesions in the large intestines were observed in the mid- and high-dose group along with presumed secondary white blood cell changes. Findings indicative of systemic toxicity, including increased kidney, liver, and spleen weight, and clinical biochemistry changes were observed in the highest dose group. Reproductive Findings: No reproduction toxicity was observed in any dose group. No changes were noted in any of the reproductive parameters investigated in this study (mating, fertility and conception indices, precoital time, and numbers of corpora lutea and implantation sites). Developmental Findings: No developmental

Table IV.D-1 Summary of Pre-Clinical Toxicological Studies on Akzo Nobel's Anti-Caking Agent [Complexation Products of Sodium Tartrates with Iron(III) Chloride]

Type of Study (Reference)	Study Details	Conclusions on Safety
	(weekly), reproduction and developmental parameters, observations pups, ophthalmoscopic examination (during pretest and Week 13), clinical pathology (end of treatment), macroscopy at termination, organ weights, and histopathology on a selection of tissues.	toxicity was observed at any dose level. No changes were noted in any of the developmental parameters investigated in this study (gestation index and duration, parturition, maternal care and early postnatal pup development consisting of mortality, clinical signs, body weight, and macroscopy). Conclusions: The following no-observed-adverse-effect levels (NOAEL) were derived: Parental local NOAEL: 500 mg/kg bw/d Parental systemic NOAEL: 1,000 mg/kg bw/d Reproduction NOAEL: at least 2,000 mg/kg bw/d Developmental NOAEL: at least 2,000 mg/kg bw/d
Mutagenicity and Genotoxicity Studies		
Bacterial reverse mutation assay (Verbaan, 2010 – unpublished)	Tester strains: *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2uvrA. Concentration: 100 to 5,000 µg/plate with or without metabolic activation.	The anti-caking agent was determined to be non-mutagenic under the experimental conditions.
Chromosomal aberration test (Buskens, 2010 – unpublished)	Test system: Human peripheral lymphocytes. Experiment 1: Concentrations of 1,000 to 5,000 µg/mL for a 3-hr exposure period with a 24-hr fixation time either in the absence or presence of metabolic activation. Experiment 2: Concentrations of 1,000 to 5,000 µg/mL for a 24-hr exposure time with a 24-hr fixation or concentrations of 300 to 1,750 µg/mL for a 48-hr exposure time with a 48-hr fixation time in the absence of metabolic activation. Concentrations of 1,000 to 5,000 µg/mL for a 3 h exposure time with a 48-hr fixation time in the presence of metabolic activation.	The anti-caking agent was determined not to be clastogenic in human lymphocytes under the different experimental conditions evaluated.
Mammalian cell gene mutation assay (Verspeek-Rip, 2011 – unpublished)	Test system: L5178Y mouse lymphoma cells. Experiment 1: concentrations of 3 to 5,000 µg/mL for a 3-hr incubation period with or without metabolic activation. Experiment 2: Concentrations of 1 to 5,000 µg/mL in the presence (3-hr incubation) or absence (24-hr incubation) of metabolic activation.	The anti-caking agent was determined not to be mutagenic in mouse lymphoma cells under the experimental conditions evaluated.

IV.E Additional Considerations

IV.E.1 Oxalic Acid

Formed as a normal degradation product of dicarboxylic acids such as tartaric acid, oxalate may occur as a manufacturing impurity of potential toxicological concern (content not more than 1.5% on dry basis, calculated as the acid; Table III.C-1). Taking into consideration the worst case scenario, where an individual consumed 11.3 g of salt per day, containing the anti-caking agent at the maximum intended use level of 12 ppm calculated as iron, exposure to oxalic acid would not exceed 18 µg/person/day. Oxalic acid occurs as a normal dietary constituent (*e.g.,* of plant-based food such as fruits, vegetables, seeds, and cereal grains), as well as an endogenous metabolite of other dietary components (citric acid, tartaric acid, ascorbic acid *etc.*). Maximum limits on the content of oxalic acid also are routinely included in specifications of additives such as citric acid, L-tartaric acid and their salts. While high dietary intakes of oxalic acid may increase urinary oxalate excretion, thus increasing the risk of calcium oxalate precipitation in the kidneys (*i.e.,* kidney stones) (Holmes *et al.*, 2001), the potential exposure to oxalic acid from its presence as an impurity in the anti-caking agent from its limited use in salt are considerable lower than that from other, more widely consumed food ingredients such as fruit juice or additives such as citric acid. Consequently, there are no safety concerns associated with the presence of oxalic acid as an impurity in the anti-caking agent.

IV.F Summary and Basis for GRAS Conclusion

Akzo Nobel intends to market the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt. The anti-caking agent is defined by its specific molar ratios of iron to *meso*-tartrate (1:1) and iron to total tartrates (1:1.5) and is manufactured as an aqueous solution containing *ca.* 35% by weight complexation products. It is intended for use as a replacement for existing substances used as anti-caking agents in salt, such as sodium ferrocyanide decahydrate, and the amount added to the salt will be that required to achieve the intended effect but not in excess of 12 ppm (0.0012%) calculated as iron.

Based on its chemical properties and confirmed analytically, the anti-caking agent will dissociate to its respective components upon ingestion. Thus, the safety assessment of the anti-caking agent under its intended use and estimated intakes was primarily based on the database of published information pertaining to the safety of the individual components, tartaric acids (Section IV.B) and iron (Section IV.C). Unpublished findings of pre-clinical toxicological studies on the anti-caking agent itself provided corroborative evidence of its safety under the intended conditions of use (Section IV.D). Together, the data provided above support the conclusion that the estimated exposures to the complexation products of sodium tartrates with iron(III) chloride under its intended conditions of use would not be expected to pose safety concerns.

Finally, the Expert Panel convened on behalf of Akzo Nobel, independently and collectively, critically evaluated the data and information summarized above and concluded that the intended use of the complexation products of sodium tartrates with iron(III) chloride produced in accordance with cGMP and meeting appropriate food-grade specifications, as an anti-caking agent in salt is safe and suitable. Furthermore, the Expert Panel unanimously concluded that the intended use of the complexation products of sodium tartrates with iron(III) chloride as an anti-caking agent in salt is GRAS based on scientific procedures. It is also the Expert Panel's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, Akzo Nobel has concluded that the complexation products of sodium tartrates with iron(III) chloride are GRAS under the intended conditions of use on the basis of scientific procedures; therefore, the anti-caking agent is excluded from the definition of a food additive and thus may be marketed and sold for the uses designated above in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

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Part	**Section §**	**Section Title**
70—Color additives	70.3	Definitions
170—Food additives	170.30	Eligibility for classification as generally recognized as safe (GRAS)
172—Food additives permitted for direct addition to food for human consumption	172.490	Yellow prussiate of soda
184—Direct food substances affirmed as generally recognized as safe	184.1077	Potassium acid tartrate
	184.1099	Tartaric acid
	184.1297	Ferric chloride
	184.1763	Sodium hydroxide
	184.1801	Sodium tartrate
	184.1804	Sodium potassium tartrate

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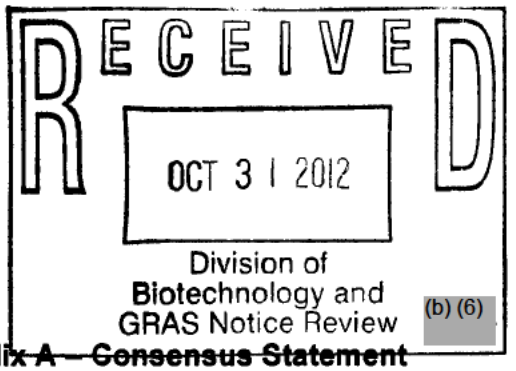

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Appendix A – ~~Consensus Statement~~

Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Iron (III) *meso*-Tartrate (Fe mTA) for Use in Foods

November 21, 2011

At the request of Akzo Nobel Industrial Chemicals BV (Akzo Nobel), an Expert Panel (the "Expert Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened (November 21, 2011), to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended for use as a food ingredient, Akzo Nobel's iron (III) *meso*-tartrate (Fe mTA) would be Generally Recognized as Safe (GRAS), based on scientific procedures. The Expert Panel consisted of the below-signed qualified scientific experts: Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor John A. Thomas, Ph.D. (Indiana University School of Medicine), and Professor Robert Nicolosi (University of Massachusetts-Lowell).

The Expert Panel, independently and collectively, critically evaluated a comprehensive package of scientific information and data pertinent to iron (III) *meso*-tartrate compiled from the literature and other published sources including opinions from regulatory through November, 2011. This information was presented in a dossier [Documentation Supporting the Evaluation of iron (III) *meso*-tartrate as Generally Recognized as Safe (GRAS) for Use in Foods, prepared by Intertek Cantox] that was submitted by Akzo Nobel to the Expert Panel. The Expert Panel evaluated data and information provided by Akzo Nobel. The Expert Panel evaluated information on the method of manufacture, product specifications and analytical data, the conditions of intended use of iron (III) *meso*-tartrate, consumption estimates for all intended uses, and a comprehensive assessment of the available scientific literature pertaining to the safety of iron (III) *meso*-tartrate.

Following independent and collective critical evaluation of such data and information, the Expert Panel unanimously concluded that under the conditions of intended use as a food ingredient described herein, iron (III) *meso*-tartrate, meeting appropriate food-grade specifications and manufactured consistent with current good manufacturing practice (cGMP), is GRAS based on scientific procedures. A summary of the basis for the Expert Panel's conclusion is provided below.

SUMMARY AND BASIS FOR GRAS

Akzo Nobel intends to market Fe mTA, which is produced as a 35% aqueous solution containing the products of a complexation reaction between sodium tartrate and iron (III) chloride, as a food ingredient for use as an anti-caking agent in salt and salt substitutes. The final Fe mTA solution contains an approximately 1:1 molar ratio of iron (III) to *meso*-tartaric acid with an approximate 1:1.5 molar ratio of iron (III) to total tartaric acid (including both DL-tartaric acid and *meso*-tartaric acid).

Fe mTA is manufactured in a two-step process, involving first the isomerization of L-tartaric acid to an equilibrium mixture of DL-tartaric acid and *meso*-tartaric acids. Addition of iron (III) chloride results in the formation of the complexation products, the nature of which are carefully controlled by using well defined manufacturing conditions. All raw materials used in the manufacturing process are food or pharmaceutical grade. The complexation products are formed *in situ* as an aqueous solution containing 35% Fe mTA, which is used directly with no further purification or concentration. Once transported to the site of salt manufacture, the solution containing *ca.* 35% Fe mTA is diluted by approximately 8-fold and within hours, added to the salt on a conveyor belt.

The analysis of 3 non-consecutive lots of Fe mTA demonstrated that the manufacturing process produces a consistent product that meets physical and chemical specifications (Appendix A). The degradation of carboxylic acids in the presence of iron (III) occurs by photochemistry and Fenton chemistry, and analogous processes would be anticipated to occur in Fe mTA. Results of stability studies on aqueous solutions of Fe mTA (35% aqueous solutions and those diluted by approximately 8-fold) indicate that Fe mTA may be stored in the dark at room temperature for up to 3 months without significant degradation. No microbial growth was identified in aqueous 35% Fe mTA solutions stored in the dark at 10°C or 60°C for 3 months. Although some microbial growth was identified visually in the solutions diluted by 8-fold for long periods of time (*i.e.*, up to 3 months) these conditions are not representative of the intended use where these solutions would be added the salt within hours of preparation. These results indicate that Fe mTA is stable under normal conditions. Efficacy studies on Fe mTA indicate that under the intended conditions of manufacture, transport and use, Fe mTA acts as an effective anti-caking agent in salt.

Fe mTA is intended for use as a replacement for existing anti-caking agents in salt or its substitutes. Fe mTA is sold as manufactured (*i.e.*, a 35% aqueous solution of Fe mTA), and would typically be diluted approximately 8-fold prior to addition to salt/salt alternatives. The levels of addition of Fe mTA would depend on a number of factors including the particle size and moisture content of the salt or substitute, but are anticipated to be between 3 and 12 ppm calculated as iron. These levels of addition are equivalent to a resultant content of 26 to 106 ppm Fe mTA, respectively in the salt (or its substitutes). Expected intakes of Fe mTA

and its constituents were estimated based on the reported consumption of salt by the population of the United States (IOM, 2004; DHHS and USDA, 2010; NCI, 2010). At the maximum intended conditions of use (106 ppm as Fe mTA), the heavy consumer (consuming 11.3 g salt/day) all-person intake of Fe mTA was estimated to be 1.20 mg/person/day or 17.1 µg/kg body weight/day for a 70 kg individual consuming salt (and its substitutes) containing 12 ppm of the anti-caking agent expressed as iron. The resulting intake of total tartaric acid and iron (III) would be 0.53 and 0.14 mg/person/day, respectively, equivalent to 7.57 and 2.0 µg/kg body weight/day for a 70 kg individual, respectively.

Similar to other iron complexes of carboxylic acids, Fe mTA is expected to dissociate into its constituents [*i.e.*, iron (III) and tartaric acid] upon ingestion. This expectation is supported by the weak Fe/tartrate interactions identified by electrospray mass spectrometry where only the individual species were identified. Additionally, progastrin-derived peptides in the gut that bind to ferric acid ions with a high affinity will facilitate the breakdown of Fe mTA by removing iron (III) from the lumen as it is produced (Baldwin *et al.*, 2001. Therefore, it is appropriate to assess the safety of Fe mTA by evaluating the toxicity of its constituents.

The primary constituents of Fe mTA [iron (III) and tartaric acid] have long histories of consumption as components of the human diet, and have been extensively reviewed by several authoritative bodies. Following a series of reviews, JECFA established an ADI of 30 mg/kg body weight/day for various tartaric acid isomers (including meso-tartaric acid). JECFA concluded that it had no safety concerns regarding tartaric acid isomers based on current levels of consumption and a 1,400-fold safety factor between the NOAEL determined in a 2-year rat study and estimated human intakes (JECFA, 1974a,b, 1977, 1978, 2000a,b). The SCF also established an ADI of 30 mg/kg body weight/day for L- and DL-tartaric acid and their sodium, potassium, and calcium salts (used as food additives) (SCF, 1991a,b). Various tartaric acid salts are affirmed as GRAS for direct addition to foods (with no limitations on the extent of their use other than cGMP), and are permitted for use as food additives in Canada (Health Canada, 2006; U.S FDA, 2011).

JECFA established a PMTDI of 0.8 mg/kg body weight/day for iron derived from all sources except iron or hydrated iron oxides used as food coloring agents and iron supplements taken during pregnancy or lactation or for specific clinical requirements (JECFA, 1983; JECFA, 2008a,b). The IOM and Health Canada also have established recommended maximum daily intakes of 45 mg iron/day (*i.e.*, a more conservative limit of 0.64 mg/kg body weight/day for a 70 kg individual) (SCF, 1993; IOM, 2001; Health Canada, 2009). In addition, various iron (III) salts are permitted for use as nutritional supplements in natural health products in Canada, and are GRAS for direct addition to foods as nutrient supplements (with no limitations on the extent of their use other than cGMP) in the U.S. (Health Canada, 2009; U.S FDA, 2011)

Tartaric acid and iron are normal components of the human diet and are consumed as food additives, fortified foods, or food supplements. Under the proposed conditions of use of Fe mTA, exposure to these constituents is not expected to make a significant contribution to the current intakes of tartrates or iron from other sources in the diet.

At the anticipated levels of intake from Fe mTA under the intended conditions of use, meso-tartaric acid is expected to have the same metabolic fate as L(+)- and DL-tartaric acids, which are largely excreted in the urine unchanged in healthy humans, (Chasseaud *et al.*, 1977; Chadwick *et al.*, 1978; JECFA, 2000a). Tartaric acid has been demonstrated to be slightly toxic following acute oral exposure in rats, mice, rabbits, and dogs, with the lowest LD_{50} reported to be 920 mg/kg body weight in rats (Locke *et al.*, 1942; Litton Bionetics, 1975). The safety of tartaric acid at the dietary level provided by Fe mTA (0.53 mg/person/day) is further supported by the results of repeated-dose studies in rats, rabbits, and dogs (Fitzhugh and Nelson, 1947; Packman *et al*, 1963; Hunter *et al.*, 1977). For rats the NOAELs identified ranged between 600 and 2,835 mg/kg body weight/day while in rabbits a NOAEL of 1,500 mg/kg body weight/day was reported. No evidence of immunotoxicity was observed following the oral administration of tartaric acid to mice at doses up to 3,000 mg/kg body weight/day for 5 days (Vollmuth *et al.*, 1989); nor was evidence of developmental toxicity reported following oral administration of 225, 215, 181, or 274 mg tartaric acid/kg body weight/day (the highest doses tested) to maternal hamsters, rabbits, rats, or mice (respectively) during fetal organogenesis (FDRL, 1973). Results of a small study in which dogs were orally administered capsules containing 990 mg tartaric acid/day for 90 to 114 days indicate that the compound may be associated with nephrotoxicity (Krop *et al.*, 1945). However, due to the lack of a control group in this study, these results provide only weak evidence of the potential renal effects of tartaric acid at high doses. No genotoxic effects were reported following the exposure of several *S. typhimurium* strains to tartaric acid at concentrations up to 10 mg/plate (in the presence or absence of metabolic activation); exposure of S. typhimurium TA 1530 and G46, Saccharomyces D3, Chinese hamster fibroblast cells, or human tissue culture cells to tartaric acid at concentrations up to 1 mg/mL; or exposure of rats to tartaric acid at doses up to 4,000 mg/kg body weight (Litton Bionetics, 1975; Ishidate *et al.*, 1984). The results of these studies demonstrate that exposure to tartaric acid resulting from Fe mTA, under the intended conditions of use, should not pose any safety concerns.

Iron is an essential nutrient, and various iron (III) salts are GRAS for use as nutritional supplements in foods with consumption only limited by cGMP (U.S FDA, 2011). Fe mTA, under the maximum intended conditions of use, would provide iron at daily levels 100 times lower than the established RDAs. Fe mTA is expected to be metabolized in a manner identical to that of other non-heme sources of iron. Exposure to iron *via* consumption of Fe mTA under the intended conditions of use will not contribute significantly to total iron intake, and does not pose a safety concern.

The pivotal safety data that supports the safety Fe mTA are the published safety data of the constituents of Fe mTA. The safety of Fe mTA was evaluated in an acute toxicity study, a subchronic and developmental toxicity study and in a series of genotoxicity studies. No adverse effects were observed in an acute toxicity study in which female rats were administered single oral gavage doses of up to 2,000 mg Fe mTA (as a 35% aqueous solution) (Van Otterdijk 2010 – unpublished study). The subchronic and developmental/reproductive effects of Fe mTA (as a 35% aqueous solution) at doses up to 2,000 mg/kg body weight/day administered by gavage were investigated in Wistar Han rats (van Otterdijk, 2011 – unpublished study). The authors determined NOAELs of 500 mg/kg body weight/day for local effects (*i.e.*, inflammatory/hyperplastic lesions and secondary hematological effects) in F_0 generation rats; 1,000 mg/kg body weight/day for systemic effects (*i.e.*, increased kidney, liver, and spleen weights and clinical biochemistry changes) in F_0 generation rats; and >2,000 mg/kg body weight/day for reproductive/developmental effects. No mutagenic or clastogenic effects were observed following the exposure of several *S. typhimurium* strains or *E. coli* WP2 uvrA to Fe mTA (as a 35% aqueous solution) at concentrations up to 5,000 µg/plate, or human lymphocytes or mouse lymphoma cells to Fe mTA (as a 35% aqueous solution) at concentrations up to 5,000 µg/mL, in the presence or absence of metabolic activation (Buskens, 2010 – unpublished study; Verbaan, 2010 – unpublished study; Verspeek-Rip, 2011 – unpublished study).

CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the data and information summarized above and conclude that the intended uses in food of iron (III) *meso*-tartrate (Fe mTA), meeting appropriate food grade specifications presented in the supporting dossier [Documentation Supporting the Evaluation of Iron (III) *meso*-Tartrate as Generally Recognized as Safe (GRAS) for Use in Foods], and produced in accordance with cGMP, are safe and suitable, and are GRAS based on scientific procedures.

It is our opinion that other qualified experts would concur with these conclusions.

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CFR Sections Referenced (Title 21—Food and Drugs)		
Part	**Section §**	**Section Title**
172—Food additives permitted for direct addition to food for human consumption	172.410	Calcium silicate
	172.430	Iron ammonium citrate
184—Direct food substances affirmed as generally recognized as safe	184.1033	Citric acid
	184.1077	Potassium acid tartrate
	184.1099	Tartaric acid
	184.1801	Sodium tartrate
	184.1804	Sodium potassium tartrate

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Appendix A

Table A-1 Chemical Specifications for Fe mTA			
Parameter		**Proposed Specification**	**Method of Analysis**
Definition			
Chemical name		Complexation products of sodium tartrate with iron trichloride	N/A
Chemical formula		$Fe(OH)_2C_4H_4O_6Na$ (nominal)	N/A
Molecular weight		261.93 (nominal)	N/A
Assay	*meso*-Tartrate	Not less than 37%, calculated as disodium salt on dry basis	IC (anion); by calculation (disodium salt on dry basis)
	D(-)- and L(+)-Tartrate	Not less than 14%, calculated as disodium salt on dry basis	IC (anion); by calculation (disodium salt on dry basis)
	Iron(III)	Not less than 8%, calculated as element on dry basis	ICP-ES
Description		Iron (III) *meso*-tartrate is manufactured as a dark green aqueous solution typically comprising *ca.* 35% by weight complexation products. The pH of a 35% aqueous solution of complexation products is between 3.5 and 3.9	Visual inspection; pH meter
Identification		Passes tests for tartrate and iron	FCC; Appendix IIIA (passes test)
Purity			
Water		Not less than 65%	Loss on drying
Chloride		Not more than 25% on dry basis	Titration
Sodium		Not more than 23% on dry basis	ICP-MS
Arsenic		Not more than 3 ppm	ISO 11885
Lead		Not more than 5 ppm	ISO 11885
Mercury		Not more than 1 ppm	ISO 11885
Oxalates		Not more than 1.5% calculated as oxalic acid on dry basis	IC (anion); by calculation (acid form on dry basis)